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RESEARCH ARTICLE

Brain volumes and white matter diffusion across the adult lifespan in temporal lobe epilepsy

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Abstract

Objective: Typical aging is associated with gradual cognitive decline and changes in brain structure. The observation that cognitive performance in mesial temporal lobe epilepsy (TLE) patients diverges from controls early in life with subsequent decline running in parallel would suggest an initial insult but does not support accelerated decline secondary to seizures. Whether TLE patients demonstrate similar trajectories of age-related gray (GM) and white matter (WM) changes as compared to healthy controls remains uncertain. **Methods**: 3D T1-weighted and diffusion tensor images were acquired at a single site in 170 TLE patients (aged 23–74 years) with MRI signs of unilateral hippocampal sclerosis (HS, 77 right) and 111 healthy controls (aged 26–80 years). Global brain (GM, WM, total brain, and cerebrospinal fluid) and regional volumes (ipsi- and contralateral hippocampi), and fractional anisotropy (FA) of 10 tracts (three portions of corpus callosum, inferior longitudinal, inferior fronto-occipital and uncinate fasciculi, body of fornix, dorsal and parahippocampal-cingulum, and corticospinal tract) were compared between groups as a function of age. **Results**: There were significant reductions of global brain and hippocampi volumes (greatest ipsilateral to HS), and FA of all 10 tracts in TLE versus controls. For TLE patients, regression lines run in parallel to those from controls for brain volumes and FA (for all tracts except the parahippocampal-cingulum and corticospinal tract) versus age across the adult lifespan. **Interpretation**: These results imply a developmental hindrance occurring earlier in life (likely in childhood/neurodevelopmental stages) rather than accelerated atrophy/degeneration of most brain structures herein analyzed in patients with TLE.

Introduction

In healthy subjects, dynamic changes in brain structure have been demonstrated with age including decline of cerebral gray (GM) and white matter (WM) volumes and fractional anisotropy (FA) observed over most of the adult lifespan.[1–3] Despite evidence from magnetic resonance imaging (MRI) studies demonstrating that patients with mesial temporal lobe epilepsy (TLE) have GM and WM abnormalities extending beyond the temporal lobes,[4–8] whether TLE patients experience brain degeneration differently than in typical aging remains uncertain.

A cross-sectional analysis of GM and WM volumes over the lifespan in TLE reported parallel age regression lines for most measurements, rejecting the hypothesis of accelerated atrophy.[9] A longitudinal study including different epileptic syndromes also showed similar rates of hippocampal and brain atrophy for TLE patients and controls after 3.5 years.[4] In contrast, data from focal epilepsies indicated global cortical thinning progressing at twice the rate of the age-related thinning in healthy individuals.[10]

Diffusion tensor imaging (DTI) parameters have also demonstrated extensive abnormalities in WM tracts beyond the temporal lobes in TLE.[5,11] Yet, the effects of age on WM tract

abnormalities observed in TLE remain largely unknown. One study predicting age from diffusion spectrum imaging in a small cohort of TLE showed that WM tracts in patients were older than the chronological age when compared to controls, particularly in patients with right-sided seizure focus.[12] Nonetheless, this does not clarify whether patients follow different WM trajectories from typical aging.

Evidence from cognitive trajectories in TLE shows that deviations of age-regression between patients and controls occurred in childhood, rather than adulthood, when the decline in patients runs in parallel to controls.[13] These findings suggest a developmental hindrance to cognition in childhood, instead of a progressive, degenerative process.[13,14]

The association between cognitive decline and both reduction of WM volume[15] and impaired network topology[16] raises the question of whether age-related rate of decline of WM microstructure in TLE patients would be similar or accelerated in comparison with the trajectories of healthy controls.[1,17] In this case, large cross-sectional studies have the advantage of spanning a wider age range, not always suitable for longitudinal studies.[9] To disentangle the effect of epilepsy from aging on brain impairment, a reasonable approach is to test the interactions between patients and controls' slopes with age.[13] Deviations between the regression curves would support different relationships between GM and WM abnormalities and disease, namely either (1) steeper slope in patients implies accelerated decline or (2) separated but parallel regression curves would suggest that the abnormalities may have initiated prior to adulthood, potentially in association with disease onset.

The purpose here was to explore age-related changes of brain volumes and DTI of 10 WM tracts in a large cohort of 170 adult TLE patients with unilateral hippocampal sclerosis (HS) and 111 healthy controls to address whether patients and controls have a similar rate of age-related volumetric loss and FA reductions.

Materials and Methods

Subjects

One hundred seventy consecutive patients with TLE and MRI findings of unilateral HS (106 women [67.6%], mean age 47 ± 11 years, 23–74 years) followed at the outpatient Epilepsy Clinic at University of Campinas were enrolled in this study. The diagnostic criteria followed the International League Against Epilepsy guidelines.[18] All the patients had a comprehensive examination, including scalp and video-EEG confirming unilateral seizures of temporal lobe origin, without history of prior neurological surgery. For all patients, clinical MRI demonstrated typical qualitative features of HS on visual analysis (reduced hippocampal volume (HV), increased T2 signal and loss of internal hippocampal architecture). These findings were further evaluated quantitatively using hippocampal volumetry and T2 relaxometry,[19] confirming MRI signs of HS in 166 of 170 subjects. In the remaining four patients, we found inaccuracies on automatic segmentation and re-examination of patients' MRI revealed a localized hippocampal atrophy associated with loss of internal structure. In all four cases, EEG confirmed unilateral seizure of mesial temporal origin and post-surgical pathology (available in one of 4 patients) confirmed HS. According to the side of HS, patients were classified as 77 with right TLE (RTLE) and 93 with left TLE (LTLE). The two patient groups were balanced for age, age at seizure onset and duration of disease, and seizure frequency, as well as for sex and initial precipitating injury (IPI) distributions (precipitant injuries were defined as a history of prolonged febrile seizures, head trauma, meningitis, meningoencephalitis, and brain infections before the seizure onset). Summary demographics for both TLE groups are shown in Table 1.

Table 1. Clinical and demographic characteristics of patients with right (RTLE) and left (LTLE) temporal lobe epilepsy patients with unilateral hippocampal sclerosis (mean ± standard deviation, [range] or median [interquartile range]).

	RTLE (N = 77)	LTLE (N = 93)	p-value[a]
Age (years)	48 ± 11, [23–73]	47 ± 11, [24–74]	1
Sex, female, n, (%)	51 (66%)	55 (34%)	0.43
Epilepsy onset (years)	14 ± 13, [0.2–62]	12 ± 10, [0–50]	0.44
Disease duration (years)	34 ± 14, [4–65]	35 ± 14, [3–59]	1
Seizure frequency, monthly	2 [3.6]	2 [4.4]	0.8
Febrile seizures, yes, n (%)	7 (9.1)	11 (11.8)	0.56
Initial precipitating insult, yes, n (%)	18 (23.4)	34 (34.4)	0.1
Ipsilateral hippocampus volume (cm^3)[a]	3.01 ± 0.51	2.97 ± 0.51	0.95
Contralateral hippocampus volume (cm^3)[a]	3.99 ± 0.42	4.03 ± 0.43	0.94

LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy.
[a]Multivariate test statistic for age, age at epilepsy onset, and disease duration: $F_{2,167} = 1.20$; test statistics for sex: $\chi^2(2) = 1.7$; frequency of febrile seizures: $\chi^2(1) = 0.3$; frequency of initial precipitant injury: seizure frequency, $U = 3663$.

For group comparisons, one hundred and eleven healthy controls were recruited to participate in this study (75 women [62.4%, mean 47 ± 12 years, 26–80 years], matched for sex [$\chi_{(2)} = 0.79$, $p = 0.44$] and age [$t(2) = -0.35$, $p = 0.35$]). These healthy volunteers had no history of neurological or psychiatric disease. All the brain imaging for controls were reviewed, and no relevant abnormalities other than aging signs were found.

Patient consent

Prior to MRI scan, all subjects signed an informed consent form approved by the Ethics Committee of University of Campinas.

MRI acquisition

Images were acquired on a Philips Achieva 3T scanner, using a standard 8-channel head coil with an optimized protocol for epilepsy investigation.[20] The protocol included coronal T2-weighted multi-echo, T1-weighted inversion recovery and fluid attenuated inversion recovery (FLAIR) coronal images perpendicular to the long axis of the hippocampus, FLAIR axial images parallel to the long axis of the hippocampus, 3D T1-weighted gradient-echo image (1 mm isotropic voxels, no gap, flip angle = 8°, TE = 2.3 ms, TR = 7 ms, matrix 240 × 240, field of view (FOV) = 240 × 240 mm^2, 6 min scan time) and a DTI sequence (spin-echo, single-shot echo planar imaging technique, SENSE R = 2 halfscan phase encoding = 0.68, voxel size = 2 × 2 × 2 mm^3 interpolated to 1 × 1 × 2 mm^3, reconstructed matrix = 256 × 256; 70 slices of 2 mm thick; TE/TR = 61/8500 ms, one non-diffusion, 32 gradient directions, b = 1000 s/mm^2, no averages, 6 min scan time).[5]

Brain volume analysis

The 3D T1-weighted images were automatically parcellated and segmented with FreeSurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu). Volumes for GM (including cortical, subcortical, and cerebellum GM), WM (excluding cerebellum), and cerebrospinal fluid (CSF, including ventricular volumes), total brain (excluding ventricles), and bilateral hippocampi were obtained, excluding the cerebellum. To compensate for differences of head sizes, each measurement (except for total brain volume) was normalized to the total intracranial volume (TIV). We found no segmentation errors on the processed images; therefore, manual correction was not required.

DTI analysis

Ten major tracts were extracted individually with a semi-automated tractography method (detailed previously by our group[17,21]) based on a deterministic approach implemented in ExploreDTI,[22] after applying signal drift, Gibbs ringing, eddy current, and motion corrections, also using ExploreDTI. The tracts included commissural tracts (corpus callosum [CC] divided in three parts: genu [GCC], body [BCC] and splenium [SCC]), association tracts (inferior longitudinal fasciculus [ILF], inferior fronto-occipital fasciculus [IFO] and uncinate fasciculus [UF]), limbic tracts (body of fornix [BFX], dorsal cingulum [dorsal-CG] and parahippocampal-CG [ph-CG]) and a projection tract (corticospinal tract [CST]).[1,21] The selection of these tracts was based on the previous findings in TLE from our group[21,23] and others.[24] FA was extracted per tract (separated in left and right for bilateral tracts) by averaging over all the voxels, counting each voxel only once. We also extracted parallel (or axial, AD) and perpendicular (or radial, RD) diffusivities to perform an ancillary analysis beyond FA.

Statistics

Clinical and demographics characterization

Demographics and clinical data between RTLE and LTLE were analyzed using chi-square for sex, and IPI distributions, Mann–Whitney tests for seizure frequency, or multivariate analysis of variance (MANOVA) for age, age at disease onset, and epilepsy duration.

Pooling left/right TLE groups and bilateral tracts

As the primary focus of this study was to evaluate age related changes and not differences between HS lateralization, we initially evaluated the impact of side on the results to determine whether it was reasonable to combine RTLE and LTLE groups as well as the left/right of six bilateral tracts into a single measurement/subject.

For brain volumes and midline tracts, MANCOVAs were applied to test TLE side (controls, RTLE and LTLE) as between-subject effect, including age, sex, and TIV (whenever appropriate) as covariates. For the six bilateral tracts, we applied repeated-measures analysis of covariance to test TLE side (controls, RTLE and LTLE) as between-subject effect and hemispheric asymmetries (ipsi- and contralateral) as within-subjects factor, with age and sex as covariates.

As expected, both RTLE and LTLE had significant differences in most brain volumes when compared to controls (all $p < 0.01$), except for no CSF increase in RTLE and GM and contralateral HV reduction in LTLE (all $p > 0.1$). There were no differences between RTLE and LTLE for any of the brain volumes studied (all $p > 0.8$).

There was also ipsi- and contralateral FA reduction in all six bilateral tracts for both RTLE and LTLE when compared to controls (all $p < 0.001$), but we found no differences between RTLE and LTLE for any of the tracts studies (all $p > 0.13$). The intra-subject (ipsi- and contralateral) analysis showed significant ($p < 0.05$) but small FA asymmetries (ranging from 0.4% to 2.5%) in dorsal-CG, IFO, and ILF for the RTLE group, in ILF and UF for LTLE patients and in the ILF tract for controls ($p < 0.001$). We found no statistically significant asymmetries in CST and ph-CG in any group (all $p > 0.09$).

Based on the demonstration of no significant asymmetries between LTLE and RTLE for all measurements and minimal FA differences between bilateral tracts, RTLE and LTLE were pooled into a single group (TLE) and a single FA value was calculated for each of the bilateral tracts, by averaging the values from each hemisphere. This resulted in reduced total number of variables and simplified between-group comparisons[23] of regressions. Therefore, we proceeded to our main analysis with two groups (TLE and controls) and 10 tracts.

Group differences and curve fitting of age effect

MANCOVAs were used to compare (1) global volumes, (2) ipsi- and contra-HV, and (3) FA (including age, sex, and TIV (whenever appropriate) as covariates) between TLE and controls.

Considering the age range of our study population and previous reports from the literature, generalized linear models were compared to evaluate the aging trajectories of the 4 volumes and FA of the 10 tracts for controls and patients, separately.[9,25] We tested linear, cubic, and quadratic fit for all variables and group combinations. We evaluated model fitting using the Akaike information criterion and residual analysis. The best models were always linear, although previous studies have shown nonlinear relationtionships for typical age-related brain changes in larger lifespans.[1,3] The linear fit represented herein might owe to the age range restricted to the adult lifespan. The significance was assessed with F tests for each regression and with t tests for each parameter. Differences between slopes of patients and controls were investigated by testing the significance of the age*group interaction term. We also tested the interactions effects of the clinical variables age of disease onset and epilepsy duration on the age regressions of the TLE group. Variables were categorized into early (<14 years) or late (≥15 years) epilepsy onset and shorter (≤36 years) or longer (>36 years) disease duration, as defined by median values. Finally, we also evaluated AD and RD versus age in order to gain further insight into the underlying source of any observed reductions of FA.[26,27]

All p-values presented were adjusted for multiple comparisons by using Holm–Bonferroni (for the post hoc comparisons) or the false discovery rate (for the age regressions) procedures, setting $p < 0.05$ as statistically significant. All the statistical analyses were performed using SPSS (version 21, IBM Corp.) and Prism (version 7.04, GraphPad).

Results

Global volumes and FA in TLE versus controls

Overall, patients differed from controls for GM, WM, total brain, and CSF volumes ($F_{4,274} = 17.3$, Pillai's trace = 0.201, $p < 0.001$). Patients had significant volume reduction of GM by 2.8% ($p = 0.006$), WM by 8.8% ($p < 0.001$), and total brain by 6.4% ($p < 0.001$), and higher CSF volume by 100% ($p < 0.001$). HV was also different from controls ($F_{2,275} = 191.2$, Pillai's trace = 0.582, $p < 0.001$), with a 28.3% smaller ipsilateral hippocampus in TLE ($p = 0.001$) and 3.6% smaller contralateral hippocampus ($p = 0.04$). Patients also differed from controls for FA in the 10 tracts ($F_{10,214} = 16.9$, Pillai's trace = 0.441, $p < 0.001$), showing reduced FA by 1.7% to 4.6% in all tracts (all $p < 0.001$).

Global volumes and FA versus age in TLE and controls

The regression estimates of brain volumes against age in the TLE group showed significant negative linear correlations of GM, WM, total brain and ipsi- and contralateral hippocampal volumes with age, and a positive correlation between CSF volume and age (all $p < 0.03$). Similarly, the control group also showed significant negative correlations with age for GM, total brain, and hippocampal volumes and a positive correlation of CSF with age (all $p < 0.01$), with WM volume not demonstrating a significant correlation ($p = 0.42$). There were no group*age significant interactions meaning that TLE and controls presented similar slopes for brain volumes (all $p > 0.24$, Table 2 and Fig. 1), however, with an offset for the TLE group showing lower GM, WM, total brain, and bilateral hippocampal volumes, and a higher CSF volume.

The linear regression of FA versus age showed significant negative linear correlations for all 10 tracts in the TLE group (all $p < 0.04$) and for 7/10 tracts in the control group (all $p < 0.02$), excluding the ph-CG, CST, and UF tracts (all $p > 0.2$, Table 3, Fig. 2). For 8/10 tracts, there were no age*groups significant interactions (all $p > 0.24$) with TLE trajectories running in parallel to those of controls with similar slopes. For the ph-CG and

Table 2. Brain volumes versus age linear regressions for controls and TLE groups.

Region	Group	Volume (mean ± SD)[a]	R^2	$\beta 1$[b]	*p*-value	Test statistic for differences in slopes	*p*-value
GM	Control	0.36 ± 0.05	0.133	−1.428	<0.001	$F_{1,277} = 0.11$	0.74
	TLE	0.35 ± 0.04	0.161	−1.576	<0.001		
WM	Control	0.34 ± 0.04	0.006	−0.293	0.42	$F_{1,277} = 1.41$	0.24
	TLE	0.31 ± 0.04	0.050	−0.826	0.004		
CSF	Control	0.01 ± 0.01	0.156	0.170	<0.001	$F_{1,277} = 0.22$	0.64
	TLE	0.02 ± 0.01	0.076	0.156	<0.001		
Total brain	Control	0.94 ± 0.11	0.029	−1.608	0.01	$F_{1,277} = 0.67$	0.41
	TLE	0.88 ± 0.1	0.086	−2.300	<0.001		
Ipsilateral HV	Control	4.17 ± 0.51	0.172	−1.46	<0.001	$F_{1,277} = 0.09$	0.76
	TLE	2.99 ± 0.51	0.028	−1.24	0.03		
Contralateral HV	Control	4.17 ± 0.42	0.121	−1.278	0.002	$F_{1,277} = 2.7 \times 10^{-4}$	0.9
	TLE	4.02 ± 0.52	0.084	−1.286	0.001		

CSF, cerebrospinal fluid; GM, gray matter; HV, hippocampal volume; WM, white matter.
[a]Brain volumes means were significantly different between patients and controls in group comparisons at $p < 0.01$.
[b]$\beta 1 \times 10^{-3}$L/year for global volumes, $\beta 1 \times 10^{-2}$ cm^3/year for hippocampal volume.

CST, significant differences in trajectories were observed ($p = 0.036$ and $p = 0.046$, respectively), with steeper FA versus age slopes for the TLE group (Table 3, Fig. 2I,J), again with an offset for the TLE group showing lower FA values across all ages, but diverges with older age.

We also investigated the effect of age of seizure onset and epilepsy duration interactions on brain volumes and FA tracts against age regressions but no significant differences were found (all $p > 0.06$, Table 4).

Age-related changes in axial and radial diffusivity

Two different patterns were observed in both controls and patients (pattern 1: increase in both axial and radial diffusivity and pattern 2: increase in radial diffusivity only). In controls, the GCC, SCC, and BFX showed higher RD and AD (all $p < 0.03$), with the BCC and IFO showing higher RD only ($p < 0.006$). In the TLE patients, the three parts of CC and BFX showed higher AD and RD (all $p < 0.01$), the dorsal-CG and ph-CG, IFO, ILF, UF, and CST showed larger RD with age (all $p < 0.05$) with no change in AD (Table 5).

Discussion

Our analysis of a large group of TLE patients with unilateral HS provides an opportunity to study aging effects on GM and WM impairment over a large age range that would not be feasible with a longitudinal study design. Herein we found: (1) significant reductions of GM, WM, total brain, and bilateral hippocampal volumes, and increase in CSF volume in TLE patients; (2) reduced FA in 10 white matter tracts in TLE patients, and (3) similar trajectories of age-related alterations between patients and controls for global GM, WM, CSF, total brain, hippocampal volumes, and FA for 8/10 WM tracts studied.

Our findings provide further evidence for a growing body of literature demonstrating extensive GM/WM abnormalities beyond the temporal lobes in TLE.[23,28–30] The findings of whole brain abnormalities are consistent with the demonstration of macroscale whole brain network disruption in TLE based on graph theoretical analysis.[31,32]

The parallel trajectories for global and regional brain volumes and microstructural WM impairment decreasing similarly with age in TLE relative to typical aging are consistent with age-related impairment in lobar cortical thickness, and both subcortical and cerebellar GM and WM volumes between TLE and controls over the lifespan.[9] In contrast to studies suggesting progressive loss of hippocampal volume in TLE,[30,33,34] our findings of progressive hippocampal atrophy with increasing age for both TLE and controls suggest that decline in TLE happens at a consistent rate to that expected with typical aging, although with an offset for TLE. While it remains controversial whether HS is a progressive condition, our results are consistent with a previous study showing hippocampal volume from TLE patients reducing with increasing age at the same pace of controls (where ipsi- and contralateral were averaged into a single measure).[9] Additionally, a metanalysis on TLE studies showed only low to moderate evidence for progression of hippocampal atrophy with disease duration and seizure frequency,[33] while most studies did not accounted for the effects of

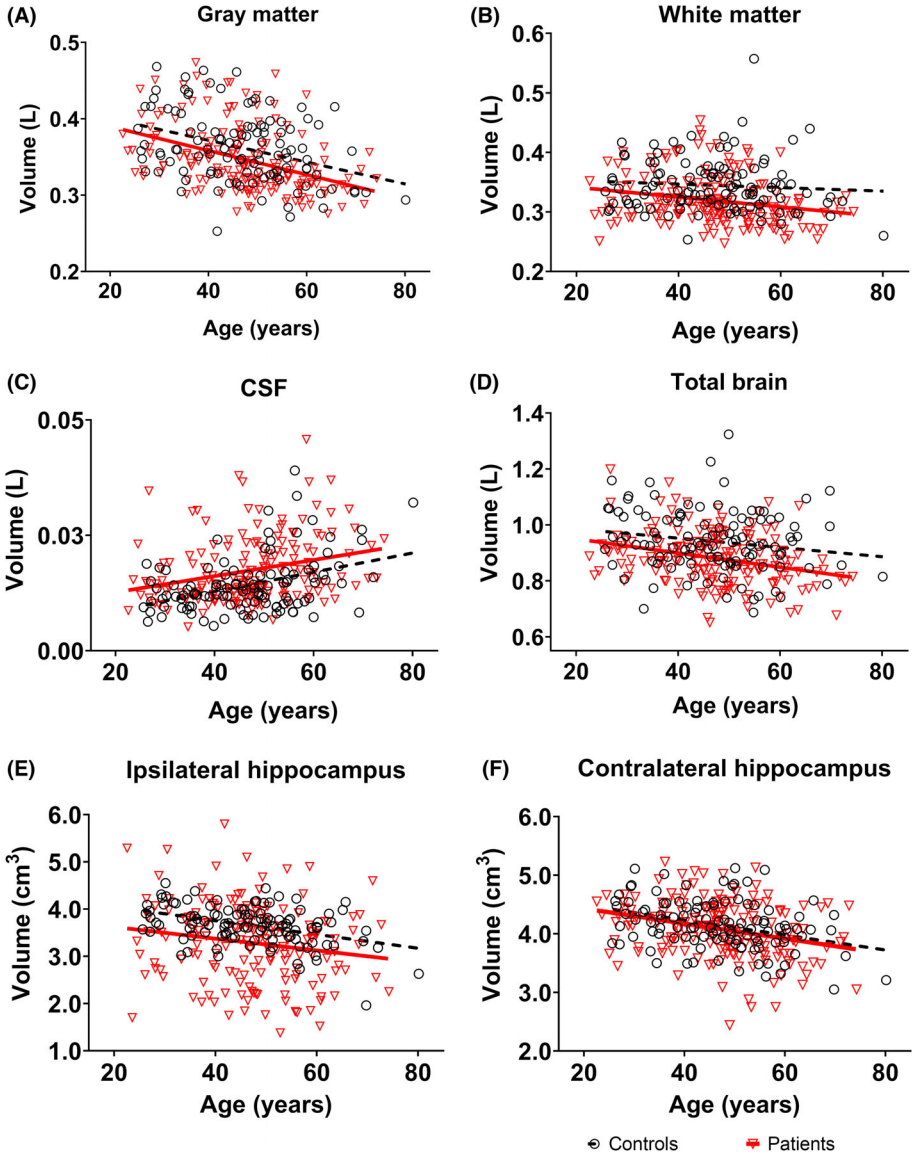


Figure 1. Linear correlations of volumes of GM (A), WM (B), CSF (C), total brain (D), and hippocampal volumes (E, F) across the adult lifespan for controls (n = 111, dashed line) and TLE patients (n = 170, solid line). TLE patients and controls yielded similar slopes but with an offset for TLE patients with lower GM, WM, and brain volumes and higher CSF volume across the age range.

chronological aging in the analysis, making it difficult to resolve disease effects from aging. Total WM volume was not significantly associated with age in controls; however, global WM volume, as an aggregate data, has been described as being less sensitive than regional FA in showing age-related impairment in healthy individuals aged 40 to 60 years.[35] This might explain the lack of significant age-related associations in WM volume of controls, while other factors beyond age (such as different health conditions over life) might better explain WM volume alterations in this group.

Likewise, the parallel trajectories for FA with age in eight out of 10 WM tracts studied (except for ph-CG and CST) during the chronic course of TLE suggest similar age-related effects to those observed for the normal controls during the adulthood. All TLE patient trajectories were also clearly separated from controls, as shown by consistently lower regression lines for TLE patients, indicating that the brain impairment in TLE might have occurred before the age range we observed in the study. These findings support the idea that for TLE patients, instead of an accelerated, degenerative condition, diffuse

Table 3. Fractional anisotropy versus age regressions for 10 WM tracts (left and right combined for six bilateral tracts) in controls and TLE.

	Group	FA (mean ± SD)[a]	R^2	$\beta 1$ ($\times 10^{-3}$)	*p*-value	Test statistics for difference in slopes	*p*-value
BCC	Control	0.57 ± 0.02	0.178	−0.630	<0.001	$F_{1,267} = 0.03$	0.86
	TLE	0.55 ± 0.02	0.150	−0.661	<0.001		
GCC	Control	0.52 ± 0.02	0.251	−0.916	<0.001	$F_{1,275} = 0.05$	0.82
	TLE	0.50 ± 0.02	0.164	−0.866	<0.001		
SCC	Control	0.57 ± 0.02	0.106	−0.425	0.004	$F_{1,272} = 0.002$	0.96
	TLE	0.56 ± 0.02	0.077	−0.417	<0.001		
BFX	Control	0.44 ± 0.02	0.070	−0.463	0.02	$F_{1,264} = 1.35$	0.24
	TLE	0.42 ± 0.02	0.127	−0.725	<0.001		
Dorsal-CG	Control	0.50 ± 0.02	0.095	−0.496	0.008	$F_{1,266} = 0.09$	0.76
	TLE	0.48 ± 0.03	0.081	−0.563	<0.001		
ph-CG	Control	0.43 ± 0.02	0.003	0.077	0.55	$F_{1,265} = 4.57$	0.036
	TLE	0.41 ± 0.02	0.040	−0.317	0.02		
IFO	Control	0.55 ± 0.02	0.194	−0.794	<0.001	$F_{1,272} = 0.4$	0.52
	TLE	0.53 ± 0.03	0.086	−0.645	<0.001		
ILF	Control	0.45 ± 0.02	0.076	−0.370	0.02	$F_{1,273} = 0.47$	0.49
	TLE	0.44 ± 0.02	0.092	−0.492	<0.001		
UF	Control	0.46 ± 0.02	0.014	−0.161	0.46	$F_{1,267} = 0.36$	0.55
	TLE	0.44 ± 0.02	0.027	−0.280	0.04		
CST	Control	0.60 ± 0.02	0.030	−0.213	0.2	$F_{1,269} = 2.84$	0.046
	TLE	0.59 ± 0.02	0.107	−0.487	<0.001		

BCC, GCC, and SCC, body, genu, and splenium of corpus callosum, respectively; BFX, body of fornix; CG, cingulum; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ph-CG, parahippocampal cingulum; UF, uncinate fasciculus.

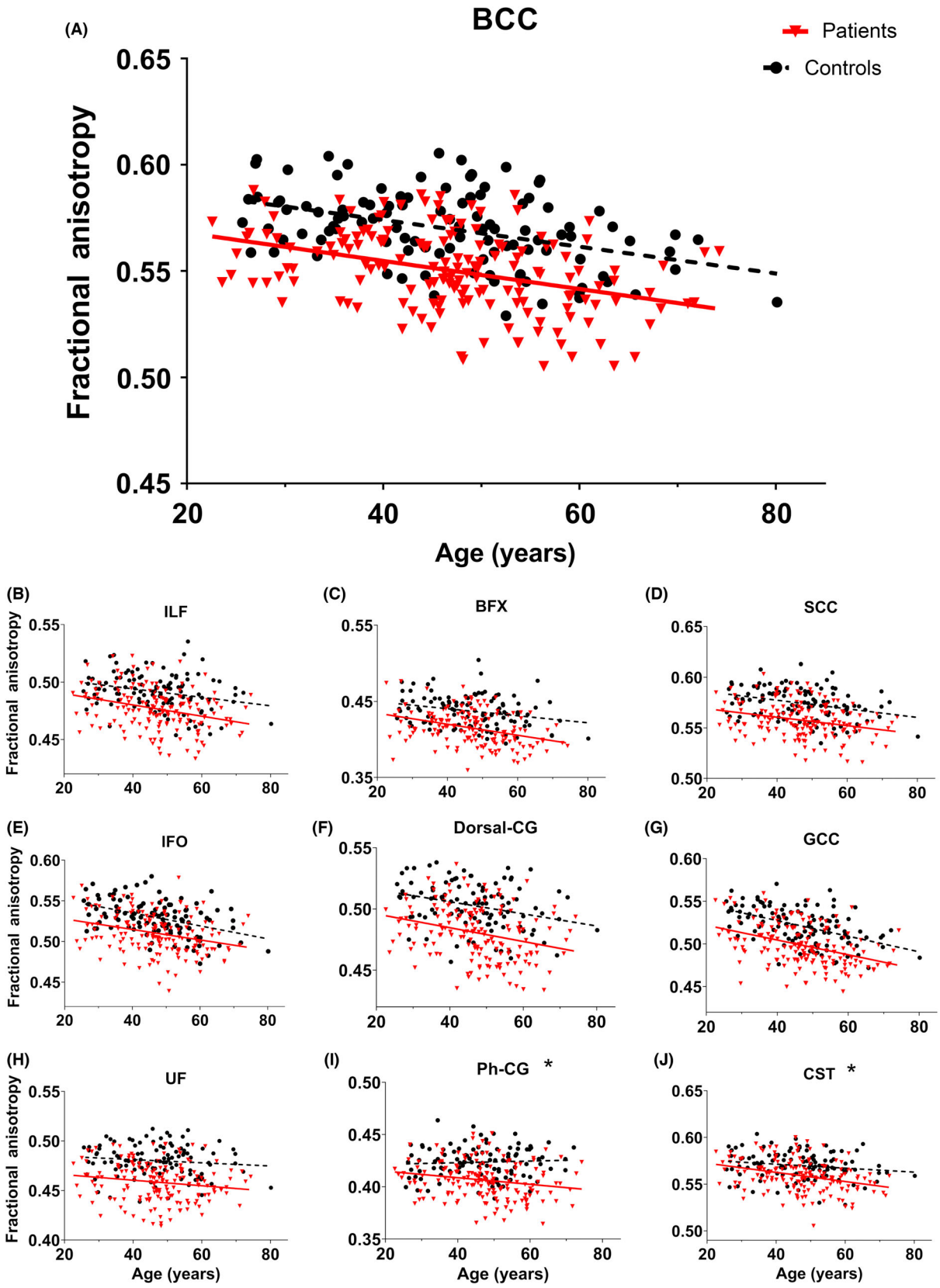
[a]FA means were significantly different between patients and controls in group comparisons for all tracts at $p < 0.001$.

whole brain structural abnormalities are present early in the disease, with age-related degeneration then following a similar trajectory to that seen with typical aging.[1,13,25,36]

In addition, these results suggest a structural basis for the observation that the decline in cognitive performance in TLE patients and controls run in parallel during adulthood.[13] One hypothesis states that a neurological disease, such as epilepsy, might "hit" an already vulnerable brain, triggering a premature cognitive aging ("second hit model"). However, after the initial "hit" the cognitive decline would then follow a pattern similar to typical aging.[37,38] Patients with epilepsy would reach their cognitive peak earlier than healthy controls, hence, reaching an earlier decline. After that, in adulthood, the cognitive trajectory between patients and controls would be similar.[13,37]

Consistent with this hypothesis and our findings, cross-sectional studies using machine-learning algorithms in MRI data have shown a gap between chronological age and the predicted "brain age" in TLE, suggesting a premature aging process of GM regions[39] and WM microstructure.[12] The only study focusing on the effects of aging in diffusion imaging found larger age gaps in WM tracts from diffusion spectrum imaging data in right-TLE,[12] mainly explained by microstructural abnormalities in the uncinate fasciculus. Nonetheless, this study tested a small cohort of TLE with HS and did not clarify whether this gap would increase or remain stable with increasing age in TLE-HS when compared to typical aging. Unlike this prior study,[12] we did not include the effect of side of HS in our models. However, Pardoe et al.[39] found increased age gap predicted from combined GM and WM volumes regardless of the presence of HS or focal cortical

Figure 2. Fractional anisotropy of white matter tracts shows linear negative correlations with age (A–G) for 10/10 tracts for TLE and 7/10 tracts for controls (except for (H) uncinate fasciculus, (I) parahippocampal cingulum, and (J) corticospinal tract). The trajectories ran in parallel over the adult lifespan (exemplified in detail in A), in both TLE patients (solid line) and controls (dashed line), except for steeper slopes in parahippocampal cingulum and CST, with an offset for TLE patients with consistently lower FA across the lifespan. BCC, GCC, and SCC, body, genu, and splenium of corpus callosum, respectively; BFX, body of fornix; CG, cingulum; ph-CG, parahippocampal cingulum; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; CST, corticospinal tract. *Significant age-by-group interactions at $p < 0.03$.


(A)
BCC
Patients
Controls
Fractional anisotropy
0.65
0.60
0.55
0.50
0.45
20
40
60
80
Age (years)
(B)
ILF
(C)
BFX
(D)
SCC
(E)
IFO
(F)
Dorsal-CG
(G)
GCC
(H)
UF
(I)
Ph-CG *
(J)
CST *

dysplasia in drug-resistant focal epilepsies,[39] indicating that the presence of a lesion is not the only factor contributing to the premature aging effect in the brain of TLE patients.

In fact, it is expected that longer disease duration would contribute to cumulative brain damage, although this relationship remains inconclusive.[33] We did not find significant interactions of disease duration and age of onset on the regressions of global and regional brain volumes and FA against age. Similarly, studies on functional[40] and GM/WM[39] premature aging did not find correlations between epilepsy duration and predicted age gap, suggesting that this gap would remain stable regardless of disease duration.

An early onset of disease in TLE has been associated with cognitive decline[41,42] and distinct degrees of thinning in different portions of the CC,[42,43] suggesting a neurodevelopment impact on WM structures at early stages,[42] although associations of onset age with GM/WM atrophy remain contradictory.[12,39,44] However, there is evidence of baseline widespread brain atrophy in children with newly diagnosed epilepsy, also pointing to neurobiological changes that might be present at early developmental stages.[45] In our study, patients with both early and late onset epilepsy had a chronic disease course while presenting similar age-related brain volumes and FA trajectories. These findings are in line with results showing both early and late epilepsy onset affecting the CC[42] and support the observed pattern of parallel GM and WM trajectories with age likely resulting from events prior or around the seizure onset (i.e., childhood or critical neurodevelopmental stages). However, it is not possible to know whether this initial "hit" is independent of seizure recurrence or it is a non-specific, though predisposing factor to epilepsy. Finally, as age at onset of epilepsy and disease duration are intrinsically correlated with age,[30] these results should be taken cautiously.

Contrariwise, there is longitudinal and cross-sectional evidence of age-related cortical thinning in TLE patients,[30] as well as longitudinal evidence of cortical thinning in focal epilepsies beyond that observed in normal aging.[10] Progression of GM and WM atrophy have

Table 4. Test statistics for epilepsy onset and duration by age interactions on brain volumes and 10 WM tract FA slopes in TLE.

	Age*epilepsy onset	*p*-value	Age*epilepsy duration	*p*-value
GM	$t = -0.84$	0.4	$t = 0.4$	0.7
WM	$t = -1.3$	0.2	$t = 0.35$	0.73
CSF	$t = 0.26$	0.98	$t = -1.5$	0.13
Total brain	$t = -0.41$	0.7	$t = -0.66$	0.51
Ipsi-HV	$t = 0.39$	0.69	$t = 0.78$	0.43
Contra-HV	$t = -0.78$	0.43	$t = 0.53$	0.59
BCC	$t = 0.45$	0.65	$t = 0.46$	0.64
GCC	$t = -0.3$	0.76	$t = 1.37$	0.17
SCC	$t = 0.3$	0.76	$t = -0.48$	0.96
BFX	$t = 0.48$	0.4	$t = -1.6$	0.11
Dorsal-CG	$t = -0.45$	0.65	$t = 0.94$	0.34
Ph-CG	$t = 1.9$	0.06	$t = 0.2$	0.98
IFO	$t = 0.81$	0.41	$t = 0.87$	0.38
ILF	$t = 1.48$	0.13	$t = 0.72$	0.47
UF	$t = -0.27$	0.78	$t = 0.91$	0.36
CST	$t = -0.26$	0.79	$t = -0.46$	0.64

BCC, GCC, and SCC, body, genu, and splenium of corpus callosum, respectively; BFX, body of fornix; CG, cingulum; contra-HV, contralateral hippocampal volume; CSF, cerebrospinal fluid; CST, corticospinal tract; GM, gray matter; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ipsi-HV, ipsilateral hippocampal volume; ph-CG, parahippocampal cingulum; UF, uncinated fasciculus; WM, white matter.

Table 5. Radial and axial diffusivity versus age regressions for 10 WM tracts (left and right combined for six bilateral tracts) in controls and TLE.

	RD $\beta 1$ ($\times 10^{-6}$)	*p*-value	AD $\beta 1$ ($\times 10^{-3}$)	*p*-value
Controls				
BCC*	**1.119**	**0.002**	0.736	0.28
GCC*	**1.611**	**0.002**	**1.139**	**0.02**
SCC*	**1.361**	**0.002**	**1.501**	**0.03**
BFX*	**3.539**	**0.002**	**4.165**	**0.005**
Dorsal-CG*	0.345	0.16	−0.666	0.16
ph-CG	0.201	0.48	0.299	0.6
IFO*	**0.793**	**0.006**	−0.643	0.28
ILF*	0.488	0.07	−0.054	0.9
UF	0.087	0.7	−0.389	0.52
CST	0.541	0.23	−0.259	0.52
TLE				
BCC*	**1.801**	**0.002**	**2.021**	**0.005**
GCC*	**2.240**	**0.002**	**2.523**	**0.005**
SCC*	**1.604**	**0.002**	**1.916**	**0.005**
BFX*	**3.139**	**0.002**	**3.039**	**0.04**
Dorsal-CG*	**0.869**	**0.002**	0.213	0.7
ph-CG*	**0.626**	**0.03**	0.233	0.7
IFO*	**1.054**	**0.002**	0.199	0.7
ILF*	**0.608**	**0.02**	−0.118	0.8
UF*	**0.512**	**0.02**	0.259	0.4
CST*	**0.555**	**0.006**	−0.528	0.07

Tracts showing significant FA versus age regressions are indicated by an asterisk. RD and AD versus age significant regressions are highlighted in boldface.

BCC, GCC, and SCC, body, genu, and splenium of corpus callosum, respectively; BFX, body of fornix; CG, cingulum; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ph-CG, parahippocampal cingulum; RD and AD, radial and axial diffusivity, respectively; UF, uncinate fasciculus.

also been associated with seizure frequency.[28] However, other studies report no significant correlations with seizure burden[4,10] and whether seizures cause brain injury in patients with TLE remains a controversial question.[13,30] Our sample had a similar seizure frequency between subgroups of HS, yet, the seizure load is just part of the complex associations underlying brain damage in epilepsy,[46] as there is also evidence of progressive GM atrophy in patients with appropriate seizure control.[34]

Whereas FA was used as the primary end point of the DTI analysis, a secondary analysis of RD and AD was performed, as they can potentially provide insight into other processes accompanying the FA changes. Exploration of specific diffusivities demonstrated two patterns in both controls and TLE: lower FA accompanied by higher RD and AD with age or lower FA accompanied by only higher RD over the adult lifespan. In TLE, the CC (three portions) and BFX showed lower FA, and higher RD and AD with age, while dorsal- and ph-CG, IFO, ILF, UF, and CST tract FA were associated with only higher RD with age. In controls, the GCC, SCC, and BFX showed lower FA followed by higher RD and AD with age, while BCC and IFO showed only higher RD over the lifespan. This is consistent with a previous finding of WM tracts showing predicted older brain age mostly driven by higher RD with less contribution from AD.[12]

It is impossible to confirm the specific microstructural changes associated with diffusion abnormalities without histology[47]; however, the differences in the patterns of diffusivity potentially suggest different microstructural changes accompanying the observed reductions in anisotropy for distinct tracts. For example, while the isolated increase in RD observed in the dorsal- and ph-CG IFO, ILF, UF could suggest demyelination, the increase in AD and RD seen in the CC and BFX would be consistent with increased extracellular space and reduced cell density.[2,27,48] Interestingly the pattern of significant abnormalities for different tracts was for the most part the same in both controls and TLE, suggesting similar aging processes for different tracts in both controls and TLE patients.

In controls, CST did not present significant age-related decline in FA, as has been described in previous studies.[12,35,49–51] In contrast, TLE patients presented significant age-related reduction of FA in CST, associated with an increase of RD. Whether the abnormalities of AD are associated with a secondary Wallerian degeneration[52] needs further investigation; however, it is noteworthy that the same pattern of changes was identified in the internal capsule of normal subjects previously.[22] Neurocognitive studies have identified age-accelerated psychomotor changes in TLE[53,54]; however, these studies did not correlate cognitive findings with structural abnormalities and were unable to characterize the neurobiology of psychomotor slowing. We can speculate that our results offer some support for these findings, as progressive deterioration of CST could result in slower motor responses.

The absence of age-related FA abnormalities of the ph-CG in controls is partially in accordance with a previous study of segments of the cingulum[55]; however, other studies have described significant age-related changes for both dorsal[1,36] and parahippocampal portions,[56] supporting the age-related observations in TLE patients.

Based on evidence confirming the relationship between the degradation of microstructure of ph-CG with age-related cognitive decline,[56] our finding of age-accelerated degradation of the ph-CG and CST is not surprising.[57,58] Similar findings have been reported in schizophrenia, suggesting the existence of common neurodegenerative process involved in pathological aging.[59]

The steeper slopes observed for the ph-CG and CST suggest accelerated degeneration in TLE patients spur further investigation into tract-specific vulnerability in TLE. While not reaching significance, age at seizure onset demonstrated a possible interaction effect ($p = 0.06$) on ph-CG FA age-regression which requires further investigation. To answer this question, it would be necessary to differentiate aging from disease progression in appropriate longitudinal cohorts.[10]

Our study is not without limitations. This is not a longitudinal analysis, and therefore, it is not possible to exclude the possibility of some cohort effect as older patients may have experienced different lifespan conditions (e.g., poorer health conditions, different medications used, and inadequate treatment early in life).[9] In fact, we found that <25% of the variance in brain volumes and FA impairment was explained by age, with weaker relationship strengths for brain volumes. A meta-analysis found only low to moderate evidence of progression of GM structures atrophy in TLE,[10] while impairment in 27 ipsi- and contralateral WM DSI-based tracts combined could explain approximately 50% of the variability in the age gap (uncinate fasciculus was responsible for 22%, with other tracts explaining up to only 9.7%),[12] suggesting that more complex interactions might also be underlying the damage observed in TLE over the adult lifespan.

We restricted our analyses to the adult lifespan, when TLE is markedly prevalent. Without information from childhood and adolescence, we can only speculate that for the tracts with parallel trajectories a developmental hindrance is most likely to be related to the persistent lower FA values observed throughout lifetime. We cannot confirm whether these subjects had failures of proper brain maturation or if any other type of insult or mechanism (including genetic or environmental) caused the structural deterioration in their early ages.

Finally, different GM regions and WM tracts other than those we analyzed here might present with a different pace of aging in TLE. Ultimately, we included hippocampal atrophy as an MRI proxy of HS and tracts knowingly altered in TLE, thus adding new information on FA trajectories in the adult lifespan.[5,8] Future studies should focus on the associations between macro- and microstructural impairment, both in vivo and histopathology, to investigate underlying mechanisms of microstructure decline with age. Longitudinal follow-up of newly diagnosed youth with TLE might help to better understand when brain changes take place, further supporting earlier intervention that could potentially change the disease course.

In conclusion, our results show that brain volumes and most of the WM tracts studied in TLE present lower, but parallel age-related lines to controls, indicating the presence of widespread GM and WM abnormalities which follow a similar trajectory to healthy controls in the adult lifespan, likely as a result of a disturbance occurring earlier in life.

Author Contributions

CLY, GCB, LRPS, FC, and DWG contributed with conception and design of the study. CLY, LRPS, GCB, ML, BMC, ACC, CB, FC, and DWG contributed with acquisition, analysis, and interpretation of data. CLY, LRPS, CGB, ML, BMC, CB, FC, and DWG contributed to manuscript/figures drafting and review.

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Conflict of Interest

The authors declared no conflict of interest.

Data Availability Statement

The dataset used to obtain these results is available from the main author upon reasonable request.

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